REVIEW

Human Milk Lipid Profiles around the World: A Systematic Review and Meta-Analysis

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ABSTRACT

Reported breast milk lipid concentrations may vary with geographical region, postnatal age, and year of sample collection. In this review, we summarized data on the concentrations of total fat, total phospholipids, cholesterol, and fatty acids in human milk worldwide and their variation according to lactation stage, study area, and sample collection year. A systematic literature search was performed using the PubMed, Embase, Web of Science, and Medline databases for English-language papers and Wanfang and China National Knowledge Infrastructure databases for Chinese-language papers. A total of 186 studies evaluating the human milk lipid profiles were included. According to random-effects models based on worldwide data, the summarized means (95% CIs) as percentages of total fat were 42.2% (41.1%, 43.3%) for SFAs, 36.6% (35.6%, 37.5%) for MUFAs, and 21.0% (19.3%, 22.7%) for PUFAs. However, the study heterogeneity was high for most types of fatty acids (I^2 > 99%). Human milk from Western countries had higher concentrations of MUFAs and 18:1n–9 (ω-9), but lower concentrations of PUFAs, 18:2n–6, 20:4n–6, 18:3n–3, 20:5n–3, 22:6n–3, and total n–6 PUFA compared with those from non-Western countries (P < 0.001–0.011). Significant lactation stage differences were observed for total fat and some individual fatty acids. The concentrations of SFAs and 16:0 were significantly negatively correlated with sampling year (P < 0.001–0.028). In contrast, a significant positive correlation between the concentrations of 18:2n–6 and 18:3n–3 and sampling year was observed (P < 0.001–0.035). Our results suggest that the pooling of data on human milk lipid profiles in different studies should be done with caution due to the high between-study heterogeneity. The concentration of lipids, including total fat, cholesterol, and specific fatty acids, differs in human milk according to lactation stage, geographical region, and year of sample collection. *Adv Nutr* 2022;13:2519–2536.

Statement of Significance: This review study compiled the published concentrations of total fat, phospholipids, cholesterol, and individual fatty acids in human milk and investigated their variation with respect to geographical area, lactation stage, and year of sample collection. We found that the pooling of data on human milk lipid profiles in different studies should be done with caution owing to the high heterogeneity across studies. The concentration of lipids, including total fat, cholesterol, and specific fatty acids, differs in human milk according to lactation stage, geographical region, and year of sample collection.

Keywords: human milk, lipids, fat, fatty acids, breastfeeding, infants

Introduction

Lipids are present in human milk in the form of fat globules, which mainly consist of triglycerides surrounded by a structural membrane composed of phospholipids, cholesterol, proteins, and glycoproteins. Fat from human milk provides ∼50–60% of the energy intake of young infants, as well as providing essential fatty acids (FAs) and fat-soluble vitamins (1). Triacylglycerols make up 98–99% of the total fat content of human milk and infant formulae. Their properties depend on the length and degree of unsaturation of the FAs esterified to the glycerol backbone (2). The most widely studied FAs in human milk are the long-chain PUFAs. Although some epidemiologic studies have found that children exposed to higher PUFA concentrations in breast milk exhibited better mental development (3, 4), others showed that extremely high concentrations of some subtypes or total PUFAs in

colostrum were associated with poor motor and cognitive scores (5), increased risks of developing allergic rhinitis and eczema (6), and other negative outcomes (e.g., sensitization, reduced lung function, and fat mass growth) (6, 7). Therefore, information on lipid profiles can provide guidance for defining optimal nutrient intakes for infants and can serve as the basis for the development of infant formulae.

Many individual studies worldwide have investigated the FAs, total fat, phospholipid, and cholesterol contents of human milk. There have also been some pooled data analyses of lipids in human milk, but these have only focused on specific FAs, like EPA and DHA (8, 9), total fat (10), or phospholipids (11). The composition of human milk changes dynamically with feeding, time of day, and lactation period. It also varies between individual mothers and between women of different ethnicities, and it is modulated by the maternal diet (12). Fat is one of the most variable nutrients in human milk. However, a consolidated lipid profile, based on multiple studies and reflecting geographical differences and changes through the progression of lactation and over different decades, is not yet available.

We conducted a systematic review and meta-analysis of studies of breast milk lipid content (fats, phospholipids, cholesterol, and FAs) to determine the lipid concentrations around the world and also applied meta-regression to evaluate whether lactation period, year of sample collection, and geographical location should be considered when analyzing the lipid content of breast milk.

Methods

Literature search and inclusion and exclusion criteria

A systematic literature search, up to March 2021, was performed using the PubMed, Embase, Web of Science, and Medline databases for English-language papers and Wanfang and China National Knowledge Infrastructure databases for Chinese-language papers. The following search terms were used: (fatty acid* OR lipid* OR fat OR phospholipid* OR cholesterol* OR triacylglyceride) AND (human milk OR breastmilk OR breast-milk OR breast milk). Further information was retrieved through a manual search of references from recent reviews (including meta-analyses) and relevant published original studies, as well as through searches of Google Scholar (https://scholar.google.com.hk/). The protocol has been registered on the INPLASY website, and the registration number is INPLASY202240079.

Study selection

Three reviewers (HC, MS, and JZ) independently extracted the data. Discrepancies were resolved by group discussions. Studies were eligible for inclusion if they reported the total fat, phospholipid, cholesterol, and/or FA composition of human milk. Studies were included in this meta-analysis if they *1*) analyzed 24-h milk samples or single samples from healthy mothers, with data reported as g/100 g or g/100 mL for total fat, phospholipids, and cholesterol, and percentage of total FAs for fatty acids; *2*) contained data presented as means or medians, with the SEM, SD, range, 95% CI, and/or interquartile range; *3*) measured FA concentrations by high-performance liquid chromatography, gas chromatography, or gas–liquid chromatography; and *4*) were written in English or Chinese. Studies were excluded if they *1*) used donor human milk samples that underwent additional processing; *2*) had samples with an unidentified type or lactation stage; *3*) pooled samples from multiple mothers or lactation stages; *4*) were maternal dietary restriction studies or studies of mothers with diseases, such as gestational diabetes, preeclampsia, or HIV; or *5*) were reviews or reported data measured using a human milk analyzer. For multiple reports from the same study, we included the most recent and/or most complete study. References from the retrieved articles were manually screened for additional eligible studies.

Data extraction and standardization

Human milk lipid profile data including the concentrations of total fat; phospholipids; cholesterol; the SFAs 6:0, 8:0, 10:0, 12:0, 13:0, 14:0, 15:0, 16:0, 17:0, 18:0, 20:0, 22:0, and 24:0; the MUFAs 16:1n–7, 18:1n–9, 20:1n–9, and 22:1n–9; and the PUFAs 18:2n–6 [linoleic acid (LA)], 18:3n–6, 20:2n–6, 20:3n–6, 20:4n–6 [arachidonic acid (ARA)], 18:3n–3 [α-linolenic acid (ALA)], 20:3n–3, 20:5n–3 (EPA), 22:6n–3 (DHA), total n–6, and total n–3 were extracted. When data were reported as the mean ± SEM, mean (95% CI), or median (interquartile range), we standardized them to the same units (mean ± SD) for further analysis. Following Wan et al. (13), we used a formula to transform medians to means and full ranges or interquartile ranges to SDs, whereas 95% CIs were transformed to SDs according to the formula recommended by the Cochrane Handbook (14). For studies with repeated observations from the same participants, the overall means and SDs incorporating all time points were calculated first and subsequently used for further analysis as recommended by the Cochrane Handbook (14).

Statistical analyses

Data analyses were performed using 2 methods. First, the inverse-variance weighting method was applied using the "rma.uni" function of the Metafor package of the statistical software R Studio (version 1.1.383, 2009–17), which has been previously validated (15). For total fat, phospholipid, cholesterol, and individual FA concentrations, the inverse-variance weighted means and 95% CIs were calculated. Heterogeneity between studies was assessed using the I^2 and

This work was funded by the Yihai Kerry Group and National Nutrition Science Research Grant (CNS-NNSRG2022-147).
Author disclosures: The authors report no conflicts of interest.
Supplemental Figures 1–20 and Supplemental Table 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: ALA, α-linolenic acid; ARA, arachidonic acid; DNL, de novo lipogenesis; FA, fatty acid; LA, linoleic acid.

τ^2 parameters (14). Fixed-effects models were used to pool data when heterogeneity was low or moderate ($I^2 < 50\%$), and random-effects models were performed when heterogeneity was high ($I^2 \geq 50\%$). A multivariate meta-regression model was applied to investigate the associations of lipid concentrations with lactation stage (colostrum: 0–6 d postpartum, transitional: 7–14 d postpartum, mature milk: ≥15 d postpartum or overall mean of repeated measures across different lactation stages), year of sample collection, and geographical region. For studies that did not report the year of sample collection, the publication year was used instead. Logarithmic or exponential transformation was performed based on the characteristics of the data so that the lower limits of 95% CIs of the predicted values would not be negative. For the geographical region, 2 groups of countries were included in the analysis. One group ("Western") includes studies from North America, Europe, Australia, and New Zealand. The second ("non-Western") includes studies from all other countries (from South America, Asia, and Africa). We also performed subgroup analysis based on lactation stages (colostrum, transitional, or mature milk) to identify potential sources of heterogeneity, and the group differences were estimated. In addition, the overall SD values were calculated based on the SDs of all eligible studies using the equations of "combining groups" recommended by the Cochrane Handbook (14) and the study of Zhang et al. (16) as follows:

a) Combined $SD^2 = [(A_1 + A_2 + A_3 + \ldots + A_i) - (M_1 \cdot n_1 + M_2 \cdot n_2 + M_3 \cdot n_3 + \ldots + M_i \cdot n_i)^2 / (n_1 + n_2 + n_3 + \ldots + n_i)] / (N - 1)$;
b) $A_i = \sum x^2 = SD_i^2 (n_i - 1) + M_i^2 \times n_i$ and
c) combined $SD = \sqrt{\frac{\sum A_i - \frac{[\sum (M_1 n_1)]^2}{N}}{N-1}}$,
d) where n_i and M_i are the number of subjects and mean value of study *i*, respectively, and SD_i is the standard deviation of study *i*.

Results

The search yielded 17,526 reports (**Supplemental Figure 1**). After reviewing the abstracts and titles, we selected 269 articles for full-text review. Of these, 183 published studies met our inclusion criteria (5, 12, 17–197), and 3 unpublished studies in China were also included. The detailed information of these studies is presented in **Supplemental Table 1**.

The lipid subtype concentrations and FA composition in human milk

As shown in **Table 1**, our analysis of 34 studies that measured the total fat in 14,984 human milk samples showed that the mean (95% CI) for total fat concentration was 3.40 g/100 mL (3.13, 3.66 g/100 mL). Eleven studies with a total of 14,216 samples reported the concentration of phospholipids in human milk. The summarized mean (95% CI) was 34.1 mg/100 mL (26.5, 41.6 mg/100 mL). For SFAs, MUFAs, and PUFAs, the mean (95% CI) values were 42.2% (41.1%, 43.3%), 36.6% (35.6%, 37.5%), and 21.0% (19.3%, 22.7%), respectively (Table 1 and **Figures 1–3**). In terms of the individual FAs, 18:1n–9 was the most abundant (32.7%; 95% CI: 31.7%, 33.7%), followed by 16:0 (22.1%; 95% CI: 21.5%, 22.7%) and then 18:2n–6 (15.3%; 95% CI: 14.4%, 16.2%), which together made up ∼70% of the total FA content. The corresponding estimates for 20:4n–6, 20:5n–3, and 22:6n–3 were 0.57% (0.53%, 0.60%), 0.13% (0.10%, 0.15%), and 0.42% (0.38%, 0.46%), respectively. The forest plots for these FAs are shown in **Supplemental Figures 2–8**. The studies included in most of the estimates had high I^2 values (97.0%–100%), indicating a high level of heterogeneity between studies (Table 1).

Variations in lipid subtype concentrations and FA composition in human milk across regions, lactation stages, and year of sample collection

Meta-regression analysis showed that the study heterogeneity could be attributed to differences across regions, lactation stages, and year of sample collection. As shown in Table 1, in comparison with nursing women in non-Western countries, those in Western countries had higher concentrations of 15:0, MUFAs, and 18:1n–9 but lower concentrations of PUFAs, 18:2n–6, 20:4n–6, 18:3n–3, 20:5n–3, 22:6n–3, and total n–6 PUFA in human milk ($P < 0.001$–0.011). In contrast, no significant regional difference was detected for SFAs ($P = 0.799$) and most other subtypes of FAs. The summarized mean values for SFAs, MUFAs, PUFAs, 16:0, 18:1n–9, 18:2n–6, 20:4n–6, 18:3n–3, 22:5n–3, 22:6n–3, and total n–6 PUFA in Western and non-Western countries were 42.7% and 41.7% (Figure 1), 39.4% and 34.2% (Figure 2), 16.2% and 25.0% (Figure 3), 22.1% and 22.1% (Supplemental Figure 2), 34.7% and 30.8% (Supplemental Figure 3), 12.8% and 18.1% (Supplemental Figure 4), 0.51% and 0.63% (Supplemental Figure 5), 0.88% and 1.29% (Supplemental Figure 6), 0.09% and 0.17% (Supplemental Figure 7), 0.33% and 0.53% (Supplemental Figure 8), and 14.6% and 21.0% (**Supplemental Figure 9**), respectively.

In different regions around the world, the summarized mean values for SFAs, MUFAs, and PUFAs ranged from 35.0% to 54.5% (**Figure 4**), 25.6% to 44.3% (**Figure 5**), and 11.9% to 27.0% (**Figure 6**), respectively. The means for 16:0, 18:1n–9, 18:2n–6, 20:4n–6, 18:3n–3, 22:5n–3, and 22:6n–3 in different regions are also listed in **Supplemental Figures 10–16**.

Table 2 lists the changes in lipid subtype concentrations and FA composition in human milk across different lactation stages. The total fat concentration in colostrum (2.34 g/100 mL; 95% CI: 2.07, 2.61 g/100 mL) was significantly lower than in transitional (3.22 g/100 mL; 95% CI: 2.91, 3.54 g/100 mL) and mature milk (3.61 g/100 mL; 95% CI: 3.37, 3.86 g/100 mL) ($P < 0.001$). Based on a limited number of studies, the cholesterol concentration in human milk significantly decreased across successive stages of lactation ($P < 0.001$). Palmitic acid (16:0) is the predominant SFA in human milk. The summarized mean (95% CI) values for 16:0 were 23.6% (22.8%, 24.5%),

TABLE 1 Subtypes of lipids and the fatty acids composition in human milk around the world

Variable	n[1]	K[2]	Mean (95% CI)	SD	I^2, %	Study regions		
						β	SE	P value[3]
Total fat, g/100 mL	34	14,984	3.40 (3.13, 3.66)	0.90	97.0	0.429	0.265	0.105
Phospholipid, mg/100 mL	11	14,216	34.1 (26.5, 41.6)	9.94	99.0	−14.9	12.7	0.243
Cholesterol, mg/100 mL	10	1198	16.0 (12.0, 20.0)	6.17	99.3	2.35	5.38	0.662
SFA, %	90	8815	42.2 (41.1, 43.3)	7.60	99.0	−0.279	1.10	0.799
6:0	20	1411	0.11 (0.06, 0.17)	0.45	99.6	−0.094	0.066	0.157
8:0	53	4482	0.20 (0.15, 0.24)	0.21	99.4	0.030	0.052	0.567
10:0	84	9942	1.29 (1.17, 1.40)	0.86	99.2	0.063	0.110	0.569
12:0	102	10,800	5.34 (4.95, 5.72)	2.88	98.9	0.586	0.381	0.124
13:0	24	2261	0.09 (0.02, 0.16)	0.14	98.9	0.130	0.092	0.158
14:0	108	11,006	6.47 (6.13, 6.81)	2.98	98.2	0.153	0.345	0.658
15:0	61	5307	0.25 (0.23, 0.28)	0.16	99.3	−0.111	0.022	<0.001
16:0	113	11,164	22.1 (21.5, 22.7)	4.74	99.0	0.400	0.584	0.494
17:0	63	8538	0.31 (0.29, 0.33)	0.34	99.1	−0.032	0.023	0.162
18:0	113	11,150	6.34 (6.13, 6.54)	2.03	98.5	−0.957	0.185	<0.001
20:0	82	7933	0.23 (0.21, 0.26)	0.27	99.2	0.011	0.024	0.647
22:0	64	6447	0.13 (0.11, 0.15)	0.17	98.5	0.041	0.023	0.078
24:0	55	6295	0.12 (0.10, 0.14)	0.11	98.6	0.045	0.020	0.027
MUFA, %	90	8711	36.6 (35.6, 37.5)	6.48	99.7	−5.56	0.805	<0.001
16:1n–7	52	6822	2.30 (2.11, 2.48)	0.93	98.9	0.059	0.194	0.760
18:1n–9	72	7473	32.7 (31.7, 33.7)	5.83	99.5	−4.55	0.983	<0.001
20:1n–9	60	5757	0.53 (0.47, 0.59)	0.37	99.3	0.009	0.051	0.868
22:1n–9	40	5526	0.18 (0.13, 0.22)	0.67	98.3	0.093	0.045	0.039
PUFA, %	58	5500	21.0 (19.3, 22.7)	7.76	99.8	8.22	1.45	<0.001
18:2n–6	113	12,433	15.3 (14.4, 16.2)	6.84	99.7	4.56	0.796	<0.001
18:3n–6	85	9672	0.17 (0.14, 0.21)	0.22	99.4	0.040	0.039	0.312
20:2n–6	73	6367	0.48 (0.43, 0.53)	0.36	99.2	0.137	0.033	<0.001
20:3n–6	99	10,702	0.44 (0.41, 0.47)	0.23	98.9	0.038	0.026	0.154
20:4n–6	117	12,485	0.57 (0.53, 0.60)	0.30	99.2	0.116	0.032	<0.001
18:3n–3	118	12,596	1.07 (0.98, 1.17)	1.00	99.6	0.326	0.098	0.001
20:3n–3	46	5579	0.11 (0.07, 0.15)	0.14	98.9	0.082	0.042	0.051
20:5n–3	95	10,288	0.13 (0.10, 0.15)	0.62	98.3	0.075	0.029	0.011
22:6n–3	115	12,204	0.42 (0.38, 0.46)	0.32	99.7	0.203	0.036	<0.001
Total n–6	75	9045	17.5 (16.1, 18.9)	7.22	100.0	6.18	1.39	<0.001
Total n–3	75	8237	1.93 (1.63, 2.23)	2.29	99.7	0.219	0.351	0.532

[1] *n:* total number of studies.
[2] K: total sample size.
[3] *P:* derived from meta-regression after adjustment for sample size, lactation stages, and year of sample collection.

21.5% (20.6%, 22.5%), and 21.5% (20.9%, 22.2%) for the colostrum, transitional, and mature milk stages ($P < 0.001$), respectively. The corresponding values for 20:4n–6 and 22:6n–3 were 0.78% (0.74%, 0.83%) and 0.59% (0.52%, 0.65%) in colostrum, respectively; 0.63% (0.57%, 0.69%) and 0.48% (0.42%, 0.55%) in transition milk, respectively; and 0.50% (0.47%, 0.53%) and 0.37% (0.33%, 0.40%) in mature milk, respectively ($P < 0.001$). No significant changes in the total SFA, MUFA, PUFA, 15:0, 17:0, 18:1n–9, 18:2n–6, 18:3n–3, or 20:5n–3 concentrations were observed between different lactation stages.

There were significant inverse associations between the concentrations of SFAs and 16:0 and year of sample collection ($P < 0.001$–0.028), that is, they were lower in more recent studies (**Figure 7**). Similar associations were detected for 15:0 and 17:0 (**Supplemental Figure 18**). In contrast, a significant positive correlation was observed between the concentrations of 18:2n–6 and 18:3n–3 and year of sample collection ($P < 0.001$–0.035). No significant change in concentration across sample collection year was detected for most of the other subtypes of fatty acids (**Supplemental Figures 17–20**).

Discussion

This study evaluated human milk lipid profiles worldwide and assessed whether the study region, lactation stage, and year of sample collection influenced the pooled estimates. The results showed substantial heterogeneity among the included studies for most of the lipid profiles. Meta-regression indicated that the study region, lactation stage, and year of sample collection significantly contributed to the variation in lipid profiles.

Several systematic reviews have previously assessed specific FAs such as EPA (20:5n–3) and DHA (22:6n–3) (8, 9), total fat (10), or phospholipids (11) in human milk. Using the mean and SD of 84 mean values from 65 studies, Brenna et al. (9) reported that the mean ± SD concentration of DHA in breast milk was 0.32% ± 0.22% and that of ARA (20:4n–6) was 0.47% ± 0.13%. Floris et al. (8) applied the inverse-variance weighted method to pooled data and

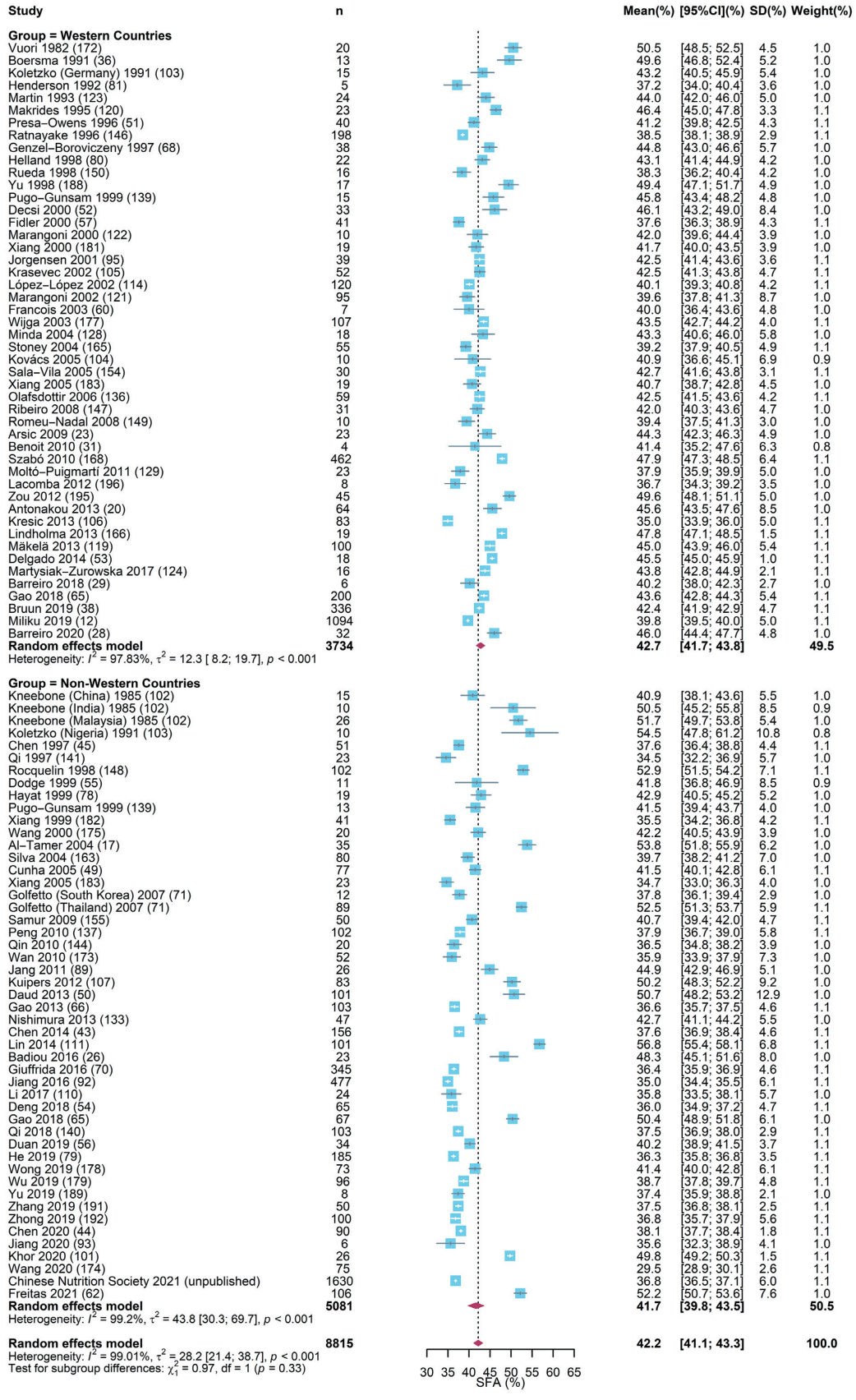

FIGURE 1 The forest plot of meta-analysis of studies assessing the concentration of SFAs in human milk. The blue squares represent the weighted mean difference in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. The red diamonds indicate the summary weighted mean difference. *n*, sample size.

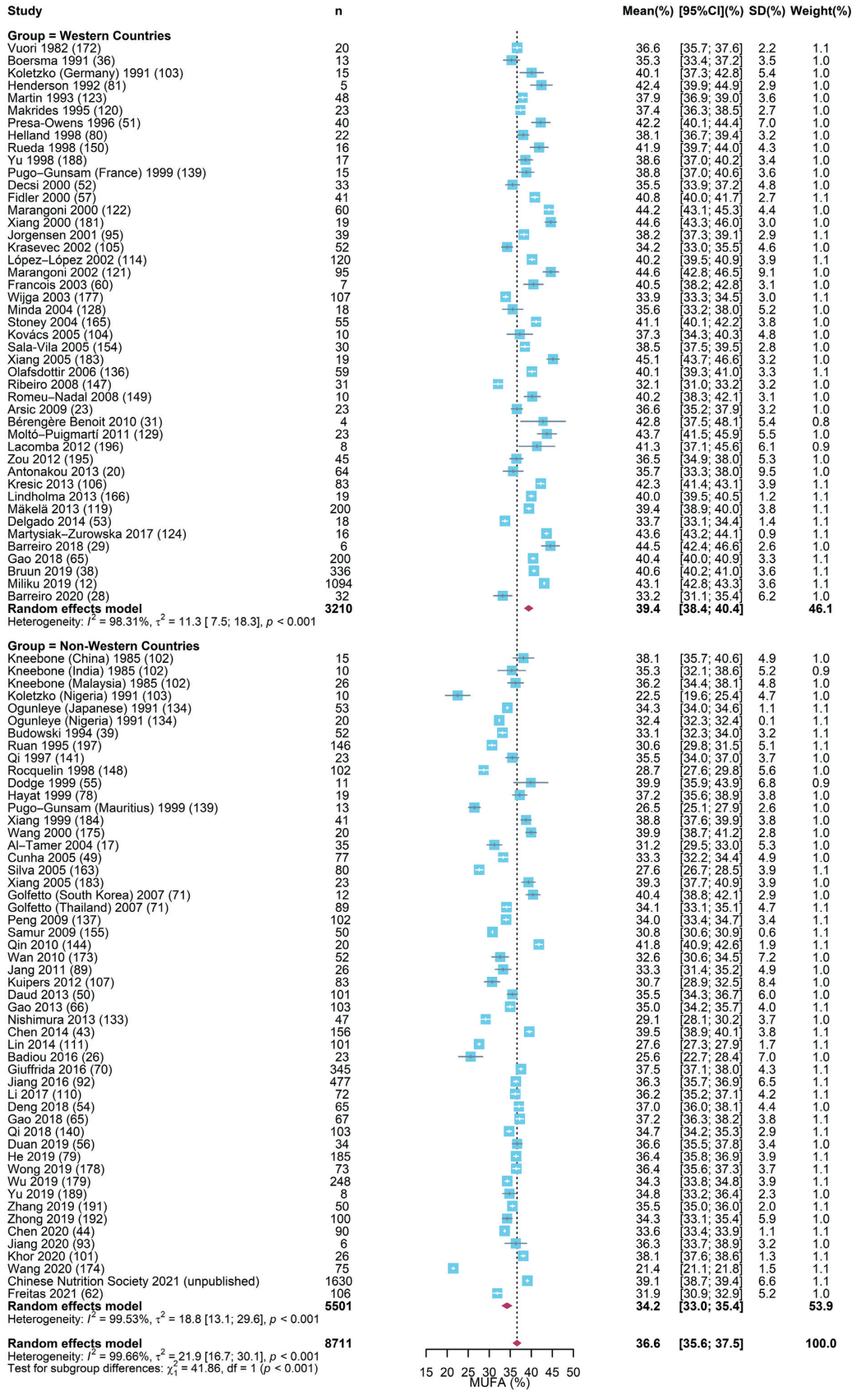

FIGURE 2 The forest plot of meta-analysis of studies assessing the concentration of MUFAs in human milk. The blue squares represent the weighted mean difference in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. The red diamonds indicate the summary weighted mean difference. *n*, sample size.

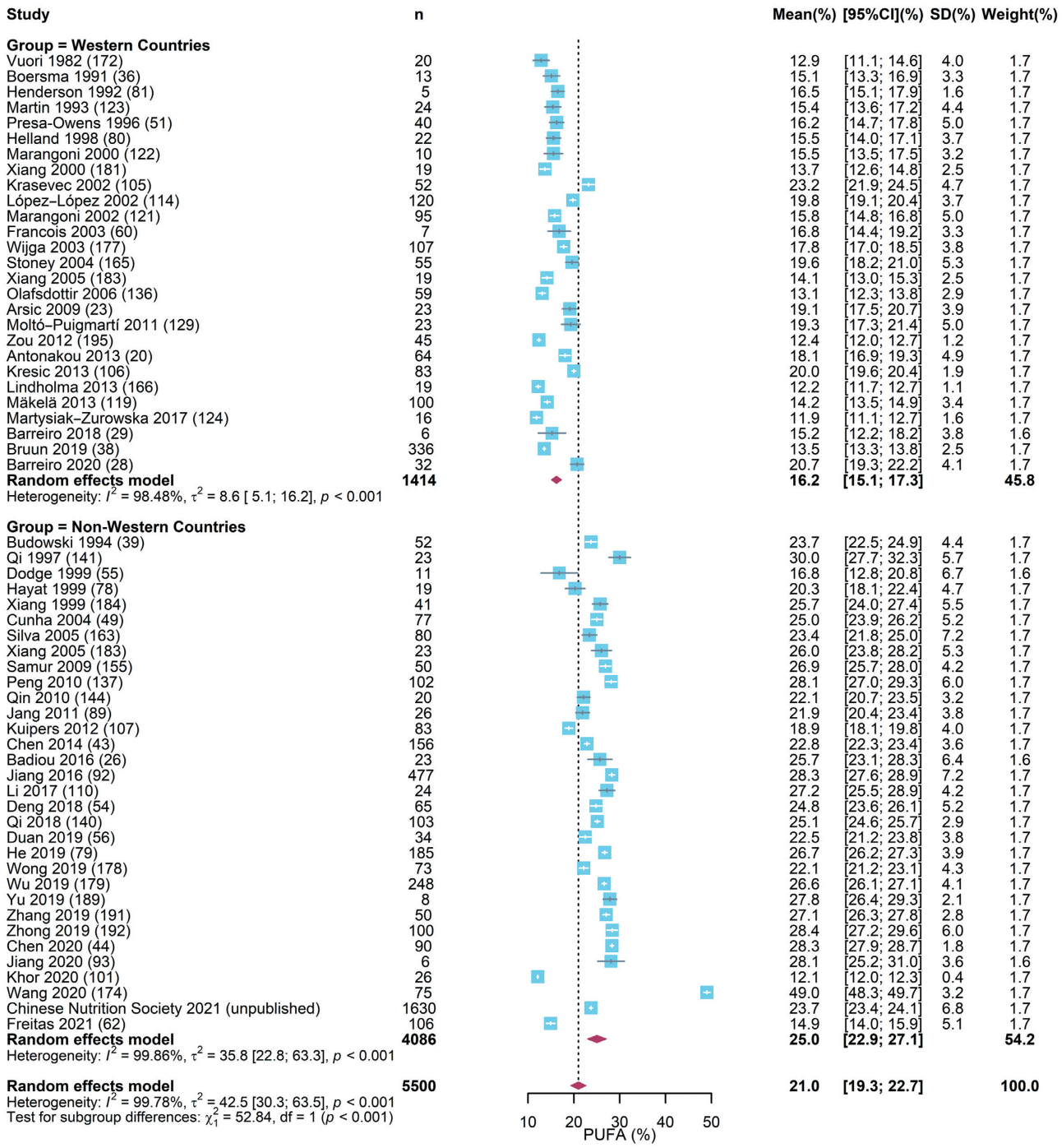

FIGURE 3 The forest plot of meta-analysis of studies assessing the concentration of PUFAs in human milk. The blue squares represent the weighted mean difference in each study, with square size reflecting the study-specific weight and the 95% CI represented by horizontal bars. The red diamonds indicate the summary weighted mean difference. *n*, sample size.

found that the mean ± SEM concentrations of DHA and ARA were 0.51% ± 0.04% and 0.77% ± 0.04%, respectively. In the present data, the mean values for those 2 FAs were 0.43% and 0.58%, respectively. Different methods for pooling data are one of the reasons for study differences. To our knowledge, ours is the most comprehensive study thus far to evaluate the composition of human milk lipids and to determine the associations between these estimates and study regions, lactation stages, and sampling year. Yuhas et al. (190) compared the FA contents of human milk across 9 countries; the ARA concentrations were reported to range between 0.36% and 0.49%, with the lowest concentration in the United Kingdom and the highest in China. In agreement with that study, we also observed that

TABLE 2 Differences in lipid subtype concentrations and fatty acid compositions across lactation stages of women throughout the world

Variable	Colostrum					Transition					Mature					*P* value[3]
	n[1]	K[2]	Mean (95% CI)	SD	I^2, %	*n*[1]	K[2]	Mean (95% CI)	SD	I^2, %	*n*[1]	K[2]	Mean (95% CI)	SD	I^2, %	
Total fat, g/100 mL	13	533	2.34 (2.07, 2.61)	1.20	89.6	13	555	3.22 (2.91, 3.54)	1.14	96.6	30	14,523	3.61 (3.37, 3.86)	0.90	96.5	<0.001
Phospholipid, mg/100 mL	8	395	43.1 (30.4, 55.7)	23.8	99.1	8	383	40.2 (28.0, 52.5)	26.0	98.7	10	13,475	30.7 (24.4, 37.0)	7.79	98.6	0.134
Cholesterol, mg/100 mL	2	48	30.9 (23.7, 38.0)	9.57	65.2	1	11	19.7 (15.6, 23.8)	7.00	NA[4]	9	1162	14.0 (11.8, 16.1)	5.55	99.1	<0.001
SFA, %	44	2406	40.0 (38.6, 41.5)	6.54	98.4	25	1524	40.6 (38.6, 42.5)	6.57	99.0	86	7754	42.2 (41.0, 43.3)	7.73	99.1	0.059
6:0	9	461	0.06 (0.02, 0.10)	0.06	99.7	6	292	0.10 (0.03, 0.16)	0.07	99.7	19	1252	0.13 (0.07, 0.20)	0.47	99.6	0.159
8:0	23	1061	0.08 (0.06, 0.10)	0.13	98.2	13	596	0.22(0.14, 0.30)	0.13	98.9	59	3833	0.21 (0.17, 0.26)	0.22	99.5	<0.001
10:0	37	2081	0.69 (0.57, 0.82)	0.50	99.7	23	1477	1.29 (1.07, 1.51)	0.64	99.5	94	8938	1.37 (1.25, 1.48)	0.86	99.4	<0.001
12:0	46	2376	3.15 (2.79, 3.50)	1.99	98.3	29	1572	5.31 (4.66, 5.97)	2.61	99.1	108	9531	5.70 (5.28, 6.11)	2.81	99.2	<0.001
13:0	11	565	0.05 (0.02, 0.08)	0.06	98.3	7	292	0.09 (0.03, 0.14)	0.09	99.0	32	1927	0.10 (0.03, 0.17)	0.15	99.3	0.345
14:0	53	2582	5.29 (4.97, 5.61)	2.01	96.2	32	1616	6.31(5.70, 6.92)	2.31	96.3	113	9653	6.56 (6.16, 6.95)	3.05	98.6	<0.001
15:0	28	1317	0.23 (0.18, 0.27)	0.18	99.2	16	781	0.21 (0.17, 0.24)	0.13	98.3	72	4465	0.25 (0.23, 0.28)	0.16	99.3	0.136
16:0	53	2589	23.6 (22.8, 24.5)	3.79	99.5	34	1636	21.5 (20.6, 22.5)	4.62	99.3	117	9838	21.5 (20.9, 22.2)	4.82	99.3	<0.001
17:0	30	2608	0.30 (0.27, 0.34)	0.51	99.0	19	1304	0.29 (0.25, 0.32)	0.36	96.7	70	5772	0.31 (0.28, 0.33)	0.15	98.8	0.656
18:0	55	2638	6.27 (5.97, 6.56)	2.20	97.7	34	1633	6.21 (5.74, 6.68)	1.82	99.2	118	9783	6.36 (6.14, 6.58)	2.07	98.7	0.810
20:0	37	1572	0.23 (0.20, 0.26)	0.15	98.0	22	929	0.25 (0.19, 0.31)	0.62	99.1	88	6798	0.23 (0.21, 0.26)	0.17	99.1	0.847
22:0	31	1385	0.14 (0.11, 0.17)	0.13	98.1	16	576	0.11 (0.09, 0.13)	0.06	98.1	72	5685	0.12 (0.10, 0.14)	0.17	98.8	0.221
24:0	30	1405	0.21 (0.17, 0.24)	0.17	97.4	17	600	0.13 (0.10, 0.15)	0.08	97.1	64	5489	0.10 (0.08, 0.11)	0.09	98.8	<0.001
MUFA, %	44	2348	37.8 (36.4, 39.1)	7.17	99.5	23	1435	35.8 (34.0, 37.6)	6.16	99.7	86	7404	36.3 (35.3, 37.4)	6.46	99.7	0.143
16:1n−7	24	1094	1.86 (1.68, 2.05)	0.76	96.4	17	614	2.09 (1.87, 2.31)	0.67	96.8	59	6432	2.3 (2.11, 2.49)	0.92	98.9	0.005
18:1n−9	35	1859	33.7 (32.3, 35.1)	7.05	99.5	25	1274	32.5 (30.8, 34.1)	7.41	99.7	75	6892	32.6 (31.5, 33.7)	5.84	99.6	0.416
20:1n−9	30	2541	0.80 (0.69, 0.91)	0.39	99.8	22	1219	0.51 (0.42, 0.60)	0.29	99.1	64	4378	0.46 (0.41, 0.50)	0.28	99.2	<0.001
22:1n−9	22	1456	0.25 (0.20, 0.29)	0.32	98.5	16	1063	0.19 (0.13, 0.24)	0.42	97.9	49	4984	0.18 (0.12, 0.23)	0.69	99.7	0.131
PUFA, %	29	1848	22.5 (19.9, 25.2)	8.71	99.8	17	1281	24.5 (20.7, 28.3)	8.43	99.9	53	4512	21.2 (19.3, 23.1)	8.18	99.8	0.287
18:2n−6	52	3395	15.3 (13.6, 17.0)	7.19	99.7	27	1482	18.0 (15.5, 20.5)	7.83	99.8	117	10,214	15.7 (14.7, 16.7)	7.15	99.7	0.193
18:3n−6	44	3369	0.12 (0.08, 0.15)	0.16	99.4	19	788	0.13 (0.09, 0.18)	0.10	98.6	85	7593	0.19 (0.15, 0.23)	0.24	99.3	0.017
20:2n−6	41	2043	0.90 (0.82, 0.99)	0.4	98.8	24	792	0.59 (0.53, 0.65)	0.23	97.6	80	5570	0.37 (0.34, 0.40)	0.19	99.4	<0.001
20:3n−6	51	3674	0.62 (0.58, 0.66)	0.24	97.2	29	1619	0.50 (0.46, 0.54)	0.21	97.9	102	8241	0.37 (0.35, 0.40)	0.18	97.9	<0.001
20:4n−6	56	3576	0.78 (0.74, 0.83)	0.29	97.9	28	1478	0.63 (0.57, 0.69)	0.24	98.7	119	10,139	0.50 (0.47, 0.53)	0.25	98.6	<0.001
18:3n−3	53	3463	0.95 (0.81, 1.10)	0.96	99.7	28	1493	1.18 (0.90, 1.47)	2.17	99.7	121	10,367	1.11 (1.00, 1.21)	1.05	99.6	0.169
20:3n−3	23	1281	0.15 (0.10, 0.20)	0.14	99.3	10	809	0.20 (0.03, 0.37)	0.22	99.2	51	4949	0.10 (0.06, 0.14)	0.12	99.2	0.171
20:5n−3	47	3174	0.14 (0.08, 0.20)	0.44	99.9	23	1167	0.16 (0.06, 0.26)	0.87	99.8	97	8366	0.12 (0.10, 0.15)	0.67	98.9	0.677
22:6n−3	54	3368	0.59 (0.52, 0.65)	0.3	98.2	31	1522	0.48 (0.42, 0.55)	0.27	97.9	118	10,083	0.37 (0.33, 0.40)	0.31	99.7	<0.001
Total n−6	37	2975	17.8 (15.6, 20.1)	8.52	99.8	21	1402	19.8 (16.6, 22.9)	8.00	99.9	69	6821	17.8 (16.2, 19.3)	7.51	100.0	0.512
Total n−3	40	3064	1.97 (1.70, 2.24)	0.87	99.9	23	1502	1.85 (1.48, 2.21)	2.41	99.9	68	5933	1.88 (1.55, 2.21)	2.63	99.8	0.846

[1] *n:* total number of studies.
[2] K: total sample size.
[3] *P:* for subgroup difference.
[4] NA: not applicable.

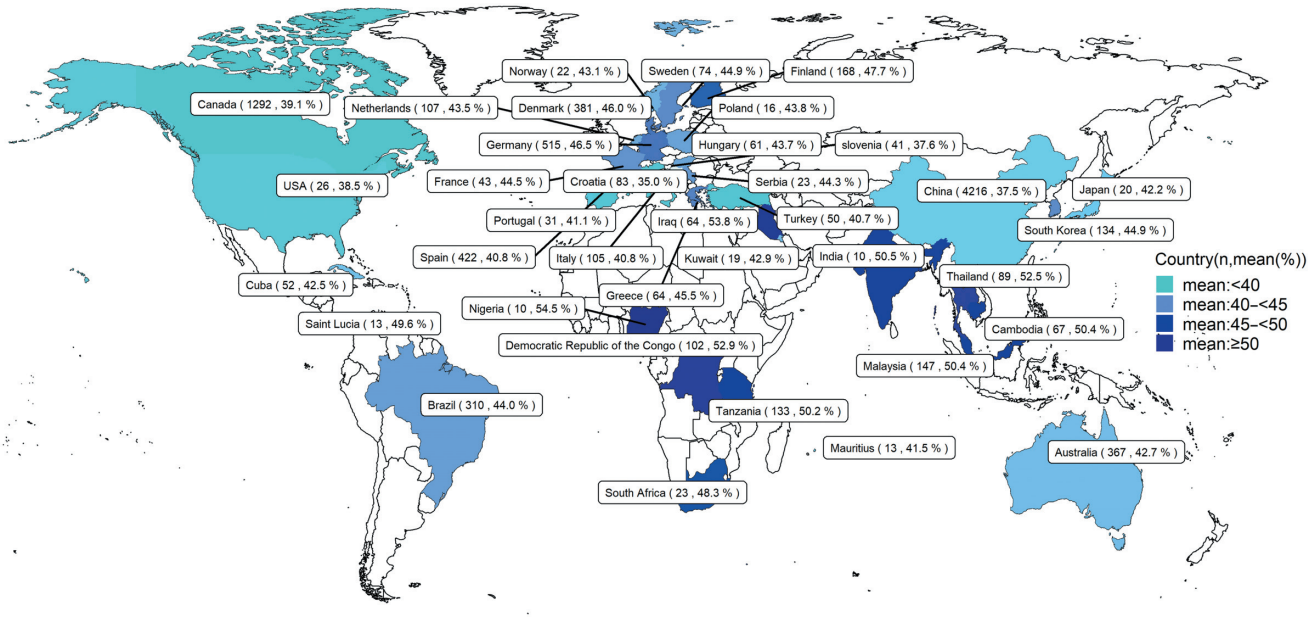

FIGURE 4 World map for the total sample size and concentration of SFAs in human milk across different countries. *n*, sample size.

region was a significant determinant of the variations in FA content. The stage of lactation is another important factor affecting the concentration of fat in human milk. Herein, the concentrations of total fat, cholesterol, and some individual FAs (16:0, 20:4n–6, and 22:6n–3) in mature milk were significantly lower than those in colostrum, which is consistent with the pooled analysis reported by Floris et al. (8).

FAs in breast milk are derived from 3 sources: the diet, adipose tissue, and endogenous synthesis. A recent review by Keikha et al. (198) reported that maternal dietary intake, particularly the intake of FAs, was related to the FA composition of breast milk (199, 200). Dietary sources of LA (18:2n–6) and ALA (18:3n–3) include flaxseeds and flaxseed oil, walnuts and walnut oil, soybeans and soybean oil, pumpkin seeds, rapeseed (canola) oil, and olive oil (201).

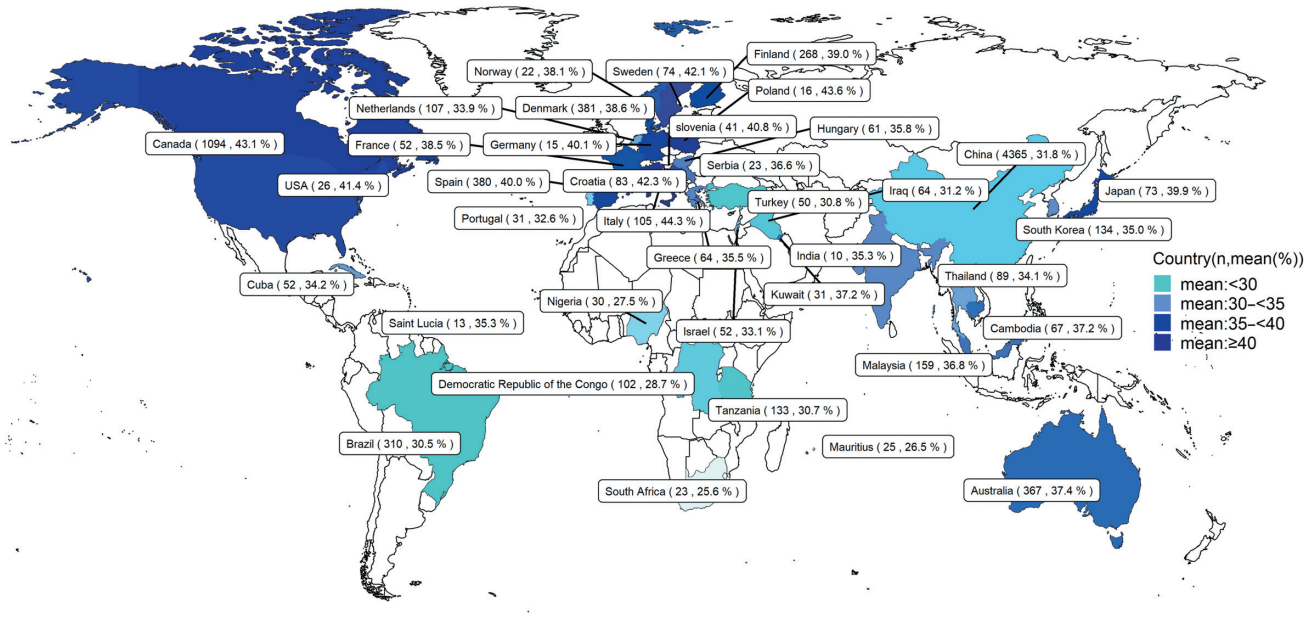

FIGURE 5 World map for the total sample size and concentration of MUFAs in human milk across countries. *n*, sample size.

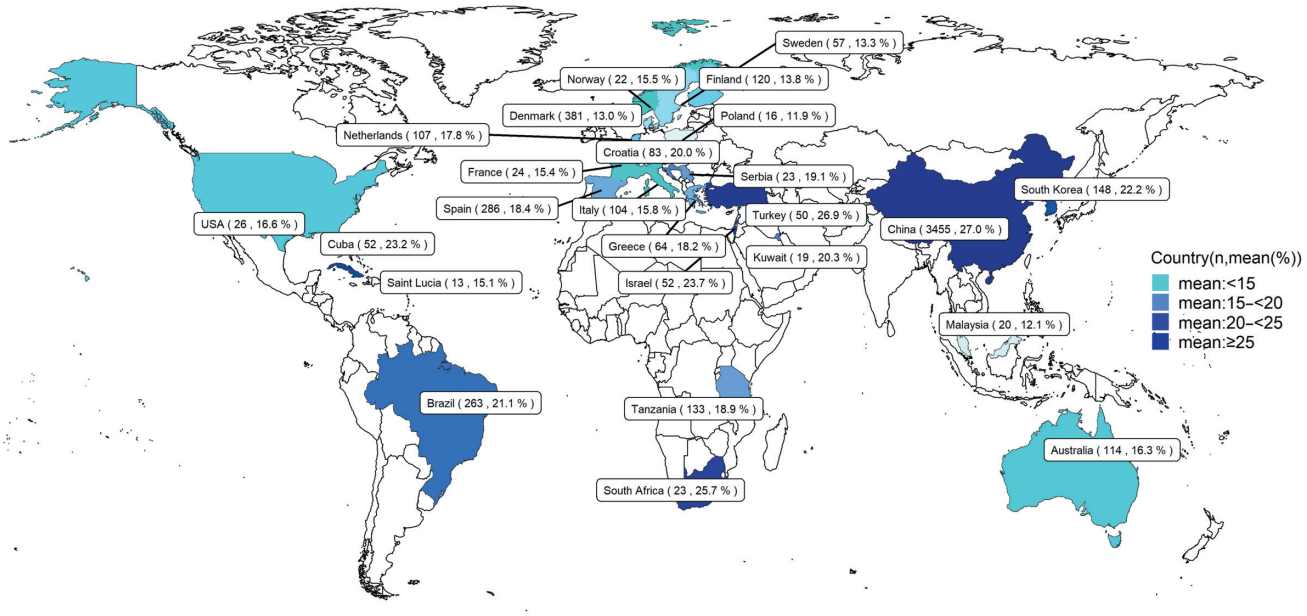

FIGURE 6 World map for the total sample size and concentration of PUFAs in human milk across countries. *n*, sample size.

The principal sources of dietary EPA and DHA are oily fish, fish oil, and certain types of seafood (202). Rich sources of dietary SFAs include butter, animal fat, and dairy products. A systematic review that analyzed FA intake data from 40 countries showed that total fat intake contributed 11.1–46.2% of energy intake, SFAs contributed 2.9–20.9%, and PUFAs contributed 2.8–11.3% (203). In a systematic analysis including 266 country-specific nutrition surveys, Micha et al. (204) reported that country-specific n–6 consumption contributed 1.2–12.5% of energy intake; meanwhile, the total consumption amounts of other fat sources were 97–440 mg/d for dietary cholesterol, 5–3886 mg/d for seafood-derived n–3, and <100–5542 mg/d for plant-derived n–3. In many places, lactating women traditionally consume considerable quantities of plant oils (e.g., in China), seafood (e.g., in Japan), or dairy products or animal foods (e.g., in Western countries), leading to a relatively high concentration of PUFAs in human milk. According to the traditional practices of postpartum care, known as *zuoyuezi* in China, mothers are encouraged to increase their intake of meat and eggs (205). The dietary practices in different postpartum periods may contribute to the variations of lipid concentrations in breast milk.

Supplement use is another source of EPA and DHA in lactating women. Using a stable-isotope method, Fidler et al. (58) observed that 2 wk of DHA supplementation resulted in an almost 2-fold increase in human milk DHA concentration (0.37% compared with 0.21%, $P = 0.003$). The total ARA concentration in human milk was found to increase with increasing ARA supplementation, from 0.4% (no ARA) to 0.49% (200 mg/d of ARA) and up to 0.56% (400 mg/d of ARA) of the total FA content at the end of the 8-wk intervention period (206). Other double-blind placebo-controlled randomized trials have also found that the concentrations of ARA and DHA in human milk are sensitive to maternal supplementation (207–209). Therefore, supplement use in different countries or lactation stages may be another reason for the lipid profile differences in breast milk. However, no information on supplement use was reported in most of the included studies in this review, so we cannot evaluate its influence.

In addition to the maternal diet, the concentrations of DHA and ARA in breast milk also depend on their level of biosynthesis from precursors. Previous intervention studies in human adults have demonstrated that the consumption of an additional 3–40 g/d ALA for 3.2–42 wk induces a –27% to 250% change in the EPA concentration and a 0% to 21% change in the DHA concentration (210). Stable-isotope studies have estimated various conversion rates of ALA into EPA, ranging from 0.2% to 8% (211). Overall, the most common dietary SFAs are 16:0 and stearic acid (18:0); however, these SFAs can also be synthesized endogenously (212).

De novo lipogenesis (DNL) is a complex and highly regulated process for the endogenous synthesis of triglycerides and other lipids from dietary starch, sugar, and protein. Palmitic acid (16:0) is the major FA product of DNL and can be elongated to stearic acid (18:0), which can then be desaturated to form palmitoleic acid (16:1n–7) or converted to oleic acid (18:1n–9) (213). Many transcription factors, such as liver X receptor, sterol regulatory element-binding protein 1c, and carbohydrate response element-binding protein exert significant control over the DNL of FAs (214). In obese individuals, hepatic lipogenesis was found to be elevated, which may contribute to their excessive fat mass (215). Large between-country differences

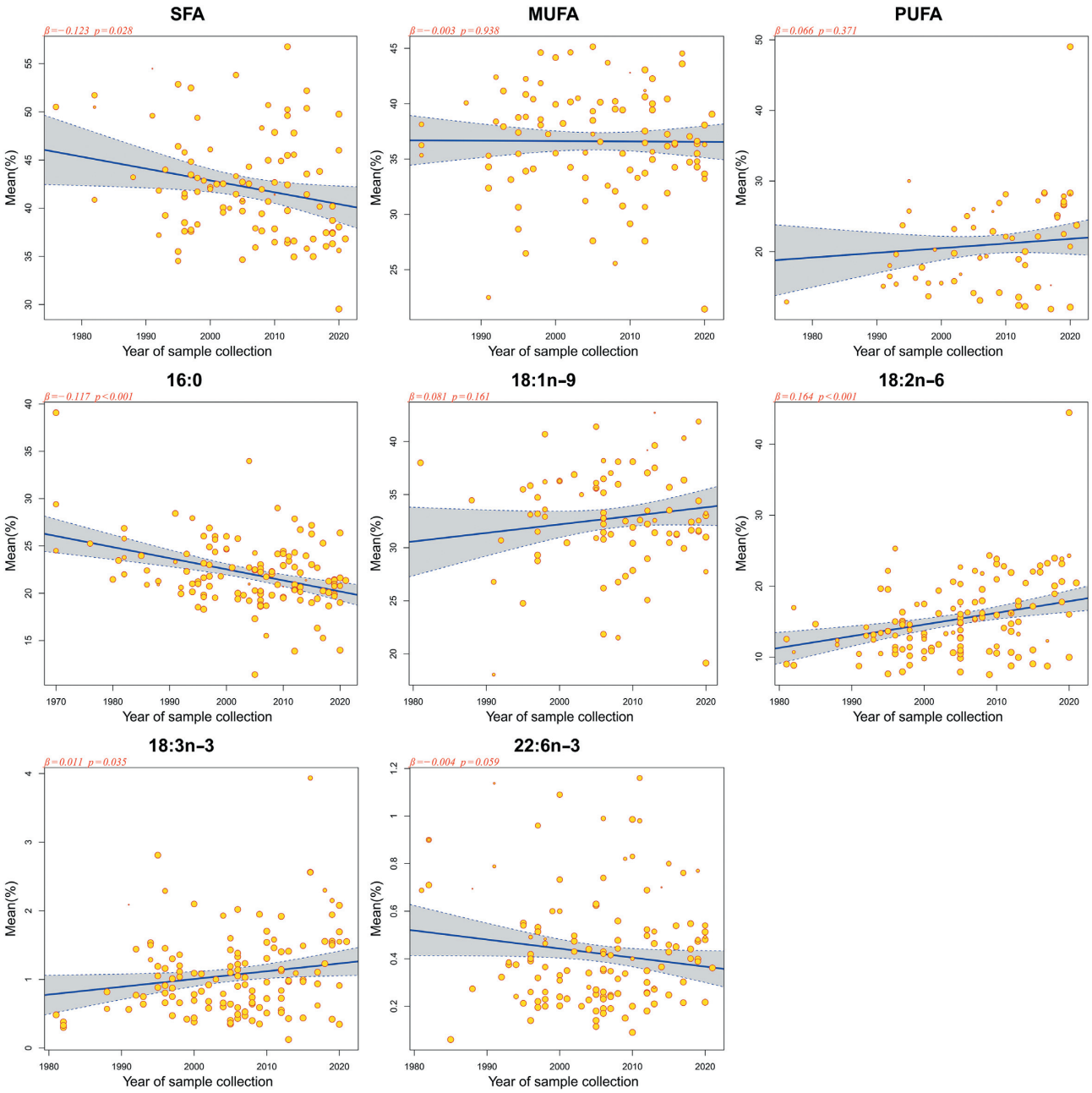

FIGURE 7 The meta-regression analysis on the relation between selected fatty acids concentration in human milk and year of sample collection. β and *P* values were derived from meta-regression analysis after adjustment for sample size, study regions, and lactation stages. Each circle represents a study, and the size of the circle represents the weight of the study.

in obesity prevalence have also been reported, from <10% to ≥25% or higher (216). Differences in carbohydrate and protein intake, weight status, and genetic background (e.g., single-nucleotide polymorphisms of the *FADS1*/*FADS2* and *ChREBP* genes) also modulate FA metabolism, leading to differences in FA concentrations (217). This is another reason for the regional variation of n–3 FA concentration. However, no study has evaluated whether the concentration of DHA and ARA biosynthesis in nursing mothers differs across lactation periods. Further studies are needed to address this issue.

Another finding of the present study was that some types of FAs varied significantly across year of sample collection. Whether the longitudinal change in human milk FA content is related to changes in the diet of nursing mothers over time has not been thoroughly investigated. Odd-chain FAs, including 15:0 and 17:0, which cannot be synthesized in humans, are considered valid biomarkers of dairy fat

intake (218). Dairy product consumption by adolescents in developed countries is reported to have declined over time (219). Consistent with that finding, we also observed a significant negative correlation between sampling year and the concentration of 15:0 and 17:0 in human milk. However, a study of Korean adults indicated that the per-capita intake of milk and dairy products (e.g., yogurt) did not significantly change from 1998 to 2010 (220). In our study, the human milk concentrations of 18:2n–6 and 18:3n–3 were also positively correlated with sample collection year. This agreed with the study by Micha et al. (204), which found that n–6, seafood-derived n–3, and plant-derived n–3 fat intakes each increased between 1990 and 2010 globally.

This study has several important strengths. First, multiple databases were systematically queried to ensure the identification of all related published studies and thus minimize the potential for publication bias and misclassification. Second, this meta-analysis had a large sample size, including 186 studies of lipid profiles in >20,000 human milk samples. Third, an investigation of the regional, lactation-stage, and longitudinal variations in the lipid content of human milk was made for the first time, to our knowledge. Fourth, 2 methods of data pooling were used, which enabled the calculation of means and CIs and also individual variation (SD values). However, several limitations of this study merit careful consideration. First, although we conducted analyses for total fat, phospholipids, cholesterol, and most subtypes of FAs, more specific subtypes of fat (e.g., *trans* fat) were not included because of the limited number of publications. Second, although we selected the studies under strict criteria, the between-study heterogeneity was still high. Except for dietary information or supplementation use, other information that may influence the lipid content of human milk such as sampling protocol, methods for FAs derivatization, and laboratory settings was also not collected (221). Thus, residual confounding in the primary studies cannot be ruled out, and the pooled data should be interpreted cautiously because of the high between-study heterogeneity.

In conclusion, this review provided a compilation of the published values of human milk lipid concentrations and investigated their variations with respect to study region, lactation stage, and year of sample collection. Our results suggest that the pooling of data on human milk lipid profiles in different studies should be done with caution due to the high between-study heterogeneity.

Acknowledgments

We thank Yan Li, Fengyan Chen, Zhen Hong, Xuanrui Zhang, Xiaoping Lin, Jiapeng Huang, and Zhaochang Huang, for their help in data checking.

The authors' responsibilities were as follows—YS and YY: contributed to the study conception and design; ZZ, YW, JZ, HC, and MS: conducted the study selection, provided data extraction, and checked the data and conducted the analysis; ZZ and YW: drafted the manuscript, which was critically revised for important intellectual content by XY, YC, HZ, and XX; and all authors: reviewed and approved the final version of the manuscript.

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